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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/711,295	11/14/2000	Vicky L. Funanage	2019659-0139	6833

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McGuire Woods
One James Center
901 East Cary Street
Richmond, VA 23219-4030

EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	7

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/711,295	FUNANAGE ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-16 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims ~~6~~ 7 and ~~11~~ 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administering leptin subcutaneously, intravenously, intramuscularly, intraperitoneally, orally, by enteral tube feeding, pulmonary delivery, intranasal delivery, controlled release delivery and pump delivery, does not reasonably provide enablement for intradermal or transdermal administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims encompass administration of leptin by various routes. Leptin is a soluble protein that is found in serum and milk and is apparently secreted by adipose tissue and placental tissue, among others. Because leptin is a soluble, secreted protein, the skilled artisan would expect that administration by routes that would involve direct administration into a fluid phase (such as intravenously) or administration into a tissue in which uptake into a fluid phase would be expected (such as intranasal or intraperitoneally), leptin would be easily taken up by the circulatory system for delivery to the lungs. However, it would not necessarily be expected that leptin would be able to be transported across the skin or under the skin and taken up by the circulatory system. Therefore, the claims are not enabled for those modes of administration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-4 and 6-16 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention. Claims 1-4 and 6-16 encompass a method for improving lung surfactant production in an individual with impaired surfactant production by administration leptin or a biologically active fragment thereof, wherein the individual may be a mammal, may be an infant with an in utero development of less than nine months, the leptin is administered in a dosage from about 0.1 ng/kg to about 100 mg/kg body weight, and may be administered orally, and wherein the step of administering the leptin compound includes administering to the individual milk fat globules containing leptin.

The claims as written read on breast-feeding. Smith-Kirwin et al., Journal of Clinical Endocrinology and Metabolism, May 1998 (cited by Applicants) teach that leptin is produced in breast milk, and that average leptin concentrations in breast milk are 73.22 +/- 39.03 ng/ml (page 1811), which is in the range of concentrations of claims 6 and 11. Smith-Kirwin et al. also teach that leptin is present in whole milk at 30- 150 fold higher concentrations than skim milk, and that leptin is secreted by mammary epithelial cells in milk fat globules. Therefore, leptin is naturally administered orally to infants who are breastfed and who may be premature and have impaired surfactant production and respiratory distress syndrome or Bronchopulmonary Dysplasia.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Torsday et al., FASEB Journal, March 15, 2000, Vol. 14, No. 4, and/or Torsday et al., Pediatric Research, 378A, March 2000, and further in view of Griese, Eurpoean Respiratory Journal, 1999 (cited by Applicants), and Halliday et al., In: Hot Topins in Neonatology, 1999 (cited by Applicants), and O'Donnell et al., Am. J. Resp. Crit. Care Med. 159, 1999 (cited by Applicant).

Claims 1-16 encompass a method for improving lung surfactant production in an individual with impaired surfactant production by administration leptin or a biologically active fragment thereof or a recombinant protein thereof, wherein the individual may be a mammal, may be an infant with an in utero development of less than nine months, the leptin is administered in a dosage from about 0.1 ng/kg to about 100 mg/kg body weight, and may be

administered orally, and wherein the step of administering the leptin compound includes administering to the individual milk fat globules containing leptin.

Griese teaches that besides a pathophysiological role for surfactant in premature infants with respiratory distress syndrome and hyaline membrane disease, a condition nowadays routinely treated with exogenous surfactant replacement, biochemical surfactant abnormalities of varying degrees have been described in obstructive lung diseases such as asthma, bronchiolitis, chronic obstructive pulmonary disease, following lung transplantation, in infectious a suppurative lung diseases such as cystic fibrosis, pneumonia, and human immunodeficiency virus, in adult respiratory distress syndrome, and other diseases, and in smokers. Halliday et al. teach that treatment of high risk preterm infants with postnatal cortiosteroids within 96 hours of birth may not outweigh the known or potential adverse effects of this treatment. Halliday et al. states"

"There was an almost significant reduction in the risk of pulmonary air leak and death or CLD (chronic lung disease) at 36 weeks in the babies treated with early corticosteroids. There were no differences in the rates of neonatal mortality, infection, severe ROP, severe IVH, NEC and pulmonary hemorrhage. Gastrointestinal bleeding and intestinal perforation were important adverse effects and the risks of hyperglycaemia and hypertension were also increased. Several adverse neurological effects were found at follow-up examinations of survivors treated with early steroids: abnormal neurological examination, cerebral palsy and developmental delay."

Torsday et al. (Pediatric Research) teach that fetal rat lung expresses leptin mRNA transcripts beginning on day c17/c18, increasing sequentially on days c19 and c20, reaching levels of 200-300% greater than baseline by day c21, and that human lung epithelial cells express the leptin receptor. Torsday et al. also teach that treatment of primary fetal rat lung type II cells with leptin (100ng/ml 24 hrs) increased the rate of surfactant phospholipid synthesis, depending upon cell type and gestational age. Torsday et al. (FASEB Journal) teach that treatment of H441

cells (human lung epithelial cells) with leptin (10 ng/ml 24 hours) results in a 140+/-30% increase in the rate of surfactant phospholipid synthesis. O'Donnell et al. teaches that obesity in humans leads to an increase in respiratory demands and increased cardiorespiratory morbidity and mortality, that obese mice which lack circulating leptin also exhibit respiratory depression, and that treatment of these mice with leptin resulted in marked increase in ventilation. Wild-type mice in which obesity is diet induced and which had respiratory depression also had ventilation compensated by administration of exogenous leptin.

It would have been *prima facie* obvious to one of ordinary skill in the art of molecular biology at the time the invention was made to increase the production of lung surfactant in respiratory conditions in which individuals have impaired surfactant production, by treatment with leptin, as taught by Torsday et al. The skilled artisan would be motivated to do so because Halliday et al. teaches that treatment with corticosteroids has not been proven effective and has serious side effects, and because Griese teaches that there are and number of respiratory diseases in which lung surfactant is deficient and needs to be enhanced or replaced. The skilled artisan would have had a reasonable expectation of success, since O'Donnell et al. teaches enhancement of respiratory function by exogenous treatment with leptin, though the mechanism of enhancement was not known.

Conclusion

5. No claim is allowed.

The definition of a biologically active fragment of leptin is found on page 12, lines 2-4 of the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner

Yvonne Eyler

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600